Materials: Highly purified rhuMAb E25 (recombinant humanized anti-IgE antibody MaE11) which did not contain TWEEN 20™ was used in the formulations described below. Spectra/Por 7 dialysis membranes were purchased from Spectrum (Los Angeles, CA). All other reagents used in this study were obtained from commercial sources and were of analytical grade. Formulation buffers and chromatography mobile phase were prepared by mixing the appropriate amount of buffer and salt with MILLI-Q™ water in a volumetric flask.

IN THE ABSTRACT OF THE DISCLOSURE:

Please replace the abstract on page 48 with the following abstract:

--A method of treating a mammal with a reconstituted formulation comprising an antibody which binds IgE is described. The formulation comprises the antibody in an amount from about 50-400mg/mL.--

REMARKS

Substitute Declaration and Cross-Reference Paragraph

Applicants submit herewith a copy of an executed substitute declaration which updates the Section 120 priority claim to USSN 08/615,369 filed March 14, 1996 (now US Patent 6,267,958) and Section 119(e) priority claim to provisional application no. 60/029,182 filed July 27, 1995. The cross-reference paragraph on page 1 is amended herein to reflect the issuance of the parent patent.

Information Disclosure

Copies of the missing references are being hand delivered to the Examiner under separate cover, along with a clean PTO-1449 form for the Examiner to initial.

A Statement of Related Cases is submitted herewith. Applicants respectfully request that the Examiner consider the related applications with regard to the present application.

Title

The title has been replaced as requested in item 6.

Abstract

The abstract has been replaced as requested in item 7.

Informalities

The trademark on page 37 at line 18 has been identified as such.

Priority

A copy of provisional application No. 60/029,182 is submitted herewith, since it is not available to the Examiner at this time. Applicants believe that the priority date of the claims herein is July 27, 1995, but note in the meantime that the statement in item 10 of the Office Action does not form the basis of any objection or rejection.

New Matter

The Examiner contends that the amendatory material that is not supported in the specification and claims as originally filed is "about 50mg/mL to about 400mg/mL."

Applicants direct the Examiner's attention to page 22, line 28 which provides written support for the claimed range. Reconsideration of the rejection is respectfully requested.

Section 102(e)

Claims 37-40 and 44 are rejected under 35 USC Section 102(e) as being anticipated by Presta *et al.* (US Patent No. 5,965,709).

Applicants respectfully request withdrawal of this 102(e) rejection. Applicants submit that the cited patent does not unambiguously set forth the presently claimed method "wherein the reconstituted formulation comprises an antibody which binds IgE in an amount of about 50 mg/mL to about 400mg/mL." While the cited patent does describe dosages of about 2 to 3 mg/kg, this disclosure does not describe the high antibody

concentration in the reconstituted formulation (*i.e.* of about 50mg/mL to about 400mg/mL).

Reconsideration and withdrawal of the rejection is respectfully requested.

Section 103(a)

Claims 37-40 and 44 are rejected under 35 USC Section 103(a) as being unpatentable over Presta *et al.* in view of Ultee *et al.* (US Patent No. 5,942,210) and/or Ressing *et al. Pharm. Res.* 9(2):266-270 (1992).

Applicants submit that the presently claimed method of treatment with a stable reconstituted anti-IgE formulation "wherein the reconstituted formulation comprises an antibody which binds IgE in an amount of about 50 mg/mL to about 400mg/mL" is patentable over the cited references.

This present invention is based, at least in part, on the discovery that a lyophilized anti-IgE antibody formulation can be prepared using a lyoprotectant (preferably a sugar such as sucrose or trehalose), which lyophilized formulation can be reconstituted to generate a stable reconstituted formulation having an anti-IgE antibody concentration which is significantly higher (*e.g.* from about 2-40 times higher) than the anti-IgE antibody concentration in the pre-lyophilized formulation. In particular, while the anti-IgE concentration in the pre-lyophilized formulation may be 5 mg/mL or less, the anti-IgE antibody concentration in the reconstituted formulation is about 50 mg/mL to about 400mg/mL. Such high antibody concentrations in the reconstituted formulation are described in the present application as being particularly useful where the formulation is intended for subcutaneous administration. Despite the high antibody concentration in the reconstituted formulation, it has been found in the present application that the reconstituted formulation is stable. (The experimental data underlying the presently claimed invention is provided on pages 37-43 of the present specification.) Prior to the present invention, the person skilled in the field of protein formulation, could not have predicted, with a reasonable

expectation of success, that the presently claimed high antibody concentration formulation could be prepared, let alone that it would be stable. In particular, before the present invention, the skilled practitioner would have been concerned that a decrease in stability of the formulation would occur as the antibody concentration was increased, *e.g.* due to increased protein aggregation in the formulation.

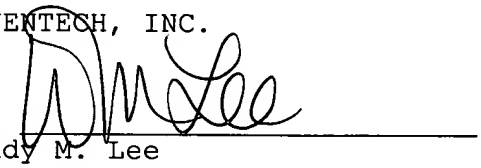
The Office has not pointed to anything in the cited references to teach the presently claimed high antibody concentration formulations. Hence, Applicants submit that the presently claimed invention is patentable over the cited art.

Reconsideration and withdrawal of the rejection is respectfully requested.

Applicants believe that this application is now in condition for allowance, and look forward to early notification to that effect.

Respectfully submitted,
GENENTECH, INC.

Date: April 19, 2002

By: 
Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE TITLE:

Please replace the title on page 1, line 5 with the following title:

[PROTEIN FORMULATION] TREATING A MAMMAL WITH A FORMULATION COMPRISING AN ANTIBODY WHICH BINDS IgE

IN THE SPECIFICATION:

Please replace the paragraph starting on page 1, line 7 with the following:

(Twice Amended) This is a divisional of application serial number 08/615,369 filed March 14, 1996 (now U.S. Patent 6,267,958 issued July 31, 2001) which claims priority under §119(e)(1) to provisional application number 60/029,182 filed July 27, 1995, both incorporated herein by reference.

Please replace the paragraph starting on page 37, line 14 with the following:

Materials: Highly purified rhuMAb E25 (recombinant humanized anti-IgE antibody MaE11) which did not contain [Tween] TWEEN 20™ was used in the formulations described below. Spectra/Por 7 dialysis membranes were purchased from Spectrum (Los Angeles, CA). All other reagents used in this study were obtained from commercial sources and were of analytical grade. Formulation buffers and chromatography mobile phase were prepared by mixing the appropriate amount of buffer and salt with [Milli-Q] MILLI-Q™ water in a volumetric flask.

IN THE ABSTRACT OF THE DISCLOSURE:

Please replace the abstract on page 48 with the following abstract:

[A stable lyophilized protein formulation is described which can be reconstituted with a suitable diluent to generate a high protein concentration reconstituted formulation which is suitable for subcutaneous administration. For example, anti-IgE and anti-HER2

antibody formulations have been prepared by lyophilizing these antibodies in the presence of a lyoprotectant. The lyophilized mixture thus formed is reconstituted to a high protein concentration without apparent loss of stability of the protein.]

A method of treating a mammal with a reconstituted formulation comprising an antibody which binds IgE is described. The formulation comprises the antibody in an amount from about 50-400mg/mL.